

AMINO ACID DISORDERS

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Outcome without screening:

The amino acid disorders are a collection of disorders that involve enzyme deficiencies that affect the metabolism of several amino acids. These deficiencies result in the increased production of intermediates that become toxic to the normal metabolic balance of the infant.

The presentation for this class of disorders varies depending on the specific amino acid affected. Severe neurological damage and in some cases death, either early in life or after several years, is the usual outcome for untreated individuals

- Alterations in the metabolism of **citrulline** lead to the classical urea cycle presentation of a toxic encephalopathy with vomiting, poor feeding, and neurological symptoms including abnormal muscle tone, seizures, and coma
- Alterations in the metabolism of **valine, leucine (and isoleucine)** also lead to the neurological progression of lethargy, seizures, coma and death
- Alterations in the metabolism of **phenylalanine** are the cause of the more well known cause of mental retardation, phenylketonuria or PKU
- Alterations in the metabolism of **methionine or tyrosine** rarely have an acute onset but may lead to long term difficulties neurologically and to a variety of organ specific failures

The newborn screen may also identify infants that have a more moderate enzyme deficiency. These infants may not have any significant clinical presentation until the stress of a severe illness or surgery produces a metabolic imbalance.

Incidence:

Based on newborn screening experience to date, each of the disorders is relatively rare except for disorders of phenylalanine metabolism which have an incidence of approximately 1 in 12,000-14,000 births.

Outcome with Screening: With the exception of the disorders of phenylalanine metabolism, these disorders are rare. There have been only a few years of experience with children identified by a newborn screen; however, evidence is accumulating that early detection and treatment can lessen the symptoms in the classic early onset cases and protect the milder cases from the repercussions of metabolic insult.

Causes of Amino Acid Disorders:

The amino acid disorders included in the newborn screen are autosomal recessive disorders that are caused by a defect in a gene that produces an enzyme necessary for the metabolic pathway of a single amino acid or a group of amino acids. In most cases, these enzymes are active primarily in the liver. The pathophysiology results from the accumulation of toxic intermediates or secondary metabolites and, in some cases, deficiency of the product.

- **Citrullinemia** is a urea cycle disorder caused by deficiency in the activity of the enzyme *argininosuccinate synthetase*. Citrulline will also be elevated as a secondary result of the deficiency of *argininosuccinic acid lyase* which results in the urea cycle disorder ***argininosuccinic aciduria***.

- **Maple Syrup Urine Disorder (MSUD)** is caused by the deficiency of the enzyme *branched chain ketoacid decarboxylase*, which is active in the metabolic pathway for three amino acids: isoleucine, leucine and valine.
- **Phenylketonuria (PKU)** is usually caused by a deficiency of *phenylalanine hydroxylase* leading to the elevation of phenylalanine. There are several subtypes of this disorder caused by deficiencies of other enzymes in the pathway. Please see the more extensive discussion of all of these disorders in the PKU section of this guide.
- **Hypermethioninemia and Homocystinuria** are two disorders that can be identified through elevated levels of methionine. Deficiency of one of two forms of *methionine adenosyl transferase* can lead to **hypermethioninemia**. *Cystathione beta synthase* deficiency leads to the more common, and more severe, disorder **homocystinuria**.
- **Tyrosinemia** includes several different disorders due to deficiency of enzymes involved in tyrosine catabolism. The most common disorder, **oculocutaneous tyrosinemia**, is due to a deficiency of *tyrosine aminotransferase*. The less frequent but clinically more severe disorder, **hepatorenal tyrosinemia**, is caused by a deficiency of *fumarylacetoacetate hydrolase*.

Screening Test and Confirmation:

In Tennessee, the newborn screen uses the plasma contained in the bloodspots collected at 24-48 hours of life. The concentration of the various amino acids or intermediates that accumulate in these disorders is measured using advanced techniques of tandem mass spectrometry. Each metabolite has a unique upper limit of normal range (cut-off) that signals the follow-up system to investigate an infant with a possible abnormal metabolic pathway. These cut-off values are set low enough that classically affected and, hopefully, mildly affected infants will be identified. Due to the natural variation in the metabolic function of newborn infants, some infants will be reported with elevated levels of metabolites that are only temporary. Thus follow-up diagnostic tests are required to identify the infants truly affected by an amino acid disorder.

Follow-up testing of infants who may be affected with one of the amino acid disorders varies from disorder to disorder. Depending on the actual level of the metabolite and the clinical presentation of the infant, a simple repeat of the newborn screen may be recommended, or more advanced diagnostic testing may be recommended. In all cases where advanced testing is required, the referral center will recommend a serum amino acid analysis. However, additional tests may be required depending on the possible disorder present in the newborn. If one or more of these tests provides support for the diagnosis of an amino acid disorder, additional enzyme analysis and possible DNA based mutation analysis may be required to finalize the diagnosis.

Treatment:

The aim of management is to

- restrict intake of precursor amino acids
- use adjunctive compounds to facilitate the clearance of toxic intermediates
- use adjunctive compounds to increase any residual enzyme activity

Specific metabolic foods are used in conjunction with commercial formula to provide the infant with the proper mixture of protein, fats, carbohydrates, and calories while still restricting intake of the specific involved amino acid. The establishment of the proper ratio of these nutrients is complex and requires the intervention of a nutritionist familiar with treatment of these disorders. Periodic evaluation of growth and amino acid intake is required to provide for optimal growth,

while maintaining the restriction of potentially toxic amino acid levels. Supplementation of the diet with vitamin cofactors and other pharmaceutical supplements may be required to improve clearance of toxic metabolites.

These infants and children are medically fragile and require long term monitoring of health and growth by educated family members, primary care providers and specialist physicians. Episodes of metabolic decompensation, that may accompany illness or medical treatments, can be devastating to the central nervous system. Any occurrence of catabolic stress requires prompt and aggressive medical intervention. In the case of **MSUD and Citrullinemia**, acute decompensation may require elimination of amino acid intake and use of adjunctive therapies such as hemodialysis to lower the levels of toxic metabolites.

Careful use of available treatments will allow the opportunity for a positive long term outlook. There is limited information available on the experiences of older children and adults who have been treated since birth. Thus clinical vigilance and treatment efforts must be considered a life-time commitment.